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# Prolonged Intravenous Therapy Versus Early Transition to Oral Antimicrobial Therapy for Acute Osteomyelitis in Children

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## What's Known on This Subject

Recent case series studies have demonstrated successful treatment of acute osteomyelitis with a short course of intravenous antimicrobial therapy followed by early transition to orally administered antimicrobial agents for a total duration of therapy of 4 to 6 weeks.

## What This Study Adds

We sought to compare the effectiveness of early transition from intravenous to oral antimicrobial therapy versus prolonged intravenous antimicrobial therapy for the treatment of children with acute osteomyelitis.

## ABSTRACT

**OBJECTIVES.** Early transition from intravenous to oral antimicrobial therapy for acute osteomyelitis in children has been suggested as a safe and effective alternative to traditional prolonged intravenous therapy via central venous catheter, but no studies have directly compared these 2 treatment modalities. We sought to compare the effectiveness of early transition from intravenous to oral antimicrobial therapy versus prolonged intravenous antimicrobial therapy for the treatment of children with acute osteomyelitis.

**METHODS.** We conducted a retrospective cohort study of children aged 2 months to 17 years diagnosed with acute osteomyelitis between 2000 and 2005 at 29 freestanding children's hospitals in the United States to confirm the extent of variation in the use of early transition to oral therapy. We used propensity scores to adjust for potential differences between children treated with prolonged intravenous therapy and logistic regression to model the association of outcome (treatment failure rates within 6 months of diagnosis) and difference in the mode of therapy within hospitals and across hospitals.

**RESULTS.** Of the 1969 children who met inclusion criteria, 1021 received prolonged intravenous therapy and 948 received oral therapy. The use of prolonged intravenous therapy varied significantly across hospitals (10%–95%). The treatment failure rate was 5% (54 of 1021) in the prolonged intravenous therapy group and 4% (38 of 948) in the oral therapy group. There was no significant association between treatment failure and the mode of antimicrobial therapy. Thirty-five (3.4%) children in the prolonged intravenous therapy group were readmitted for a catheter-associated complication.

**CONCLUSIONS.** Treatment of acute osteomyelitis with early transition to oral therapy is not associated with a higher risk of treatment failures and avoids the risks of prolonged intravenous therapy through central venous catheters. *Pediatrics* 2009;123:636–642

**E**ACH YEAR IN the United States, 1 in 5000 children under the age of 13 years is diagnosed with osteomyelitis, which accounts for 1% of all pediatric hospitalizations.<sup>1,2</sup> Osteomyelitis is a bacterial infection of the bone that can occur in children of all ages and usually requires hospitalization for diagnosis and initial management. Although osteomyelitis can result from penetrating trauma or spread from a contiguous site of infection, the most common mechanism of infection in children is hematogenous inoculation of the bone during an episode of bacteremia (acute hematogenous osteomyelitis).

Treatment of acute osteomyelitis requires prolonged administration of antimicrobial agents. Inadequately treated osteomyelitis can result in progression to chronic infection and loss of function of the affected bone. Until recently,

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### Key Words

osteomyelitis, therapy, children

### Abbreviations

PHIS—Pediatric Health Information System  
CHCA—Child Health Corporation of America  
ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*  
OR—odds ratio  
CI—confidence interval

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experts recommended that children with acute osteomyelitis receive 4 to 6 weeks of intravenous therapy, usually administered through a central venous catheter. However, recent case series studies have demonstrated successful treatment of acute osteomyelitis with a short course of intravenous antimicrobial therapy followed by early transition to orally administered antimicrobial agents for a total duration of therapy of 4 to 6 weeks. Potential advantages of this treatment strategy include lower cost, increased convenience, and reduced risk of complications associated with prolonged insertion of central venous catheters.<sup>3-8</sup> Studies to date have not quantified the degree of variation in the use of early transition to oral therapy across hospitals and the possible association of the use of early transition to oral therapy and treatment failure.

## METHODS

### Design

We performed a retrospective cohort study to compare the use of early transition to oral versus prolonged intravenous antimicrobial therapy in a large sample of children hospitalized and treated for acute osteomyelitis at 29 freestanding children's hospitals across the United States and the association of therapy and treatment failure.

### Data Source

We used the Pediatric Health Information System (PHIS), an administrative database that contains inpatient data from 40 freestanding children's hospitals affiliated with the Child Health Corporation of America (CHCA [Overland Park, KS]). Contributing hospitals are located in 17 of the 20 major metropolitan areas in the United States and account for 70% of all freestanding children's hospitals in the United States (data from the National Association of Children's Hospitals and Related Institutions, Alexandria, VA). The database includes detailed information on demographics, diagnoses, procedures, medications, and repeat hospitalizations. Included in the medication files are data on the type and route of administration of all antimicrobial agents administered during hospitalization. Oversight of PHIS data quality and accuracy is a joint effort among the CHCA, Thomson Healthcare (the data manager), and participating hospitals. Data are deidentified at the time of data submission and subjected to 175 reliability and validity checks. Data are accepted into the database when classified errors occur in <2% of a hospital's quarterly data.

### Assembly of Study Cohort

Our study included children ages 2 months to 17 years with discharge dates between January 1, 2000, and June 30, 2005. Children were included in the study cohort if their index hospitalization was assigned an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code for acute osteomyelitis or unspecified osteomyelitis (730.01-730.09 and 730.2-730.29) in any of the 21 diagnosis fields. Children with a hospitalization for chronic osteomyelitis in the 6 months before the index admission were excluded. In addition, children were

excluded if they were discharged during time periods when CHCA deemed hospital data as invalid or missing.

To define a cohort of children with uncomplicated, acute osteomyelitis, we excluded children with specific comorbid conditions documented on the index or previous admissions and those who were hospitalized for  $\geq 10$  days. Exclusionary comorbid conditions included those whose presence suggests complicated or difficult-to-treat osteomyelitis; congenital and acquired immunodeficiencies; sickle cell disease, trauma, osteomyelitis associated with immobilization, or pressure ulcers (eg, spina bifida, quadriplegia, paraplegia, mechanical ventilation, and postoperative infections); and osteomyelitis of the head, face, and orbits. We also excluded children with conditions that would predispose to inadequate absorption of oral medications (eg, malabsorption).

In addition, we excluded children with an ICD-9-CM code for any of the following conditions during any admission before study entry that might have increased the risk of subsequent complicated osteomyelitis: cellulitis, pyogenic arthritis, sacroiliitis, synovitis, myositis, chronic sinusitis, arthropathy, congenital or acquired diseases of bone, fasciitis, postoperative wounds, or placement of orthopedic devices or prosthesis. Finally, we excluded children with <6 months of observation time after the initial admission for osteomyelitis to allow adequate time for the observation of study outcomes.

### Exposure Classification

Children were classified into 1 of 2 possible treatment groups at the time of discharge from the hospital: prolonged intravenous antimicrobial therapy or early transition to oral antimicrobial therapy. The prolonged intravenous therapy group was defined by the presence of a procedure code of 38.93 (venous catheterization, not elsewhere classified), which represents the placement of a central venous catheter. Children without procedure code 38.93 were assumed to have been discharged on oral therapy and composed the early transition to oral therapy group. We assumed that transition to oral therapy occurred at the time of discharge, which may represent the most conservative estimate of transition time. The assignment of children to the prolonged intravenous or early transition to oral therapy groups was validated by CHCA as part of a data validation project using a 10% random sample of the study cohort from 19 of the 29 hospitals that agreed to participate in the validation study. The charts of children included in the validation sample were reviewed to confirm placement of a central venous catheter during the index hospitalization or early transition to oral antimicrobial therapy as part of the discharge plan.

### Outcome Measures

The primary outcome was treatment failure, defined as rehospitalization within 6 months with assigned diagnosis or procedure codes consistent with (1) acute osteomyelitis as the sole diagnosis (730.0-730.09), (2) chronic osteomyelitis (730.1X), (3) a potential complication of acute osteomyelitis (eg, myositis, arthritis, etc), or (4) a surgical pro-

cedure related to the musculoskeletal system. Secondary outcomes included rehospitalization within 6 months for (1) any reason, (2) catheter-related complication, and (3) adverse drug reactions associated with antibiotics, *Clostridium difficile* infection, or agranulocytosis, a not-uncommon effect of  $\beta$ -lactam antibiotics. To determine the outcomes, 2 of the authors (Drs Zaoutis and Keren), who were blinded to treatment group assignment, reviewed the ICD-9-CM diagnosis and procedure codes for all of the children who were rehospitalized during the study period.

### Covariates

We extracted data from the PHIS database on the following potential confounders and effect modifiers: age, gender, race, surgical procedure, anatomic location of the infection, and the presence of an ICD-9-CM code for *Staphylococcus aureus* infection or methicillin-resistant *S aureus*. We also collected information on the severity of initial illness using the PHIS case mix index, a widely used risk-adjustment measure based on relative weights derived from Thomson Healthcare's national pediatric charges per case data and 3M All-Patient-Refined Diagnosis-Related Group classification system. The relative weights are computed as the ratio of the average charges per patient in an All-Patient-Refined Diagnosis-Related Group/severity of illness group with the average charges for all other children.

### Statistical Analysis

Summary statistics were constructed using frequencies and proportions for categorical data elements and means and medians for continuous variables. The  $\chi^2$  test was used for unadjusted comparisons between children who received prolonged intravenous therapy and children who received oral therapy. Random-effects models and likelihood ratio tests were used to determine the significance of interhospital variation in the use of oral therapy, as well as in treatment failure rates. A propensity score model was developed to balance patient-level confounders that may have determined the selected treatment strategy. Propensity score analysis attempts to identify children who are similar except for their treatment or exposure status. The scores represent the probability that a patient will receive a treatment strategy based on his or her observed covariates.<sup>9,10</sup> We calculated propensity scores using multivariable logistic regression with early transition to oral therapy as the outcome of interest. Scores were then grouped into quintiles for later use as covariates in the analysis of mode of administration and treatment failure. In the response model (a logistic regression with early rehospitalization as the outcome and quintile of propensity score as a covariate), we introduced singly each covariate from the propensity score to identify any residual confounding from that covariate.<sup>11</sup> All of the confidence intervals (CIs) were adjusted for the clustering of children within a hospital using robust variance estimates.<sup>12</sup>

To determine the effect of exposure misclassification on the observed association between mode of antimicrobial administration and treatment failure, we compared

results for the subset of hospitals that participated in the validation study and had no misclassification of exposure with results for the hospitals that did not participate in the validation study or were found to have some degree of misclassification of the exposure identified in the validation study.

We performed additional analyses to determine the within- and among-hospital effects. Confounding by hospital can occur when both the exposure of interest and outcome are clustered by hospital. To address this potential problem, we decomposed the within- and among-hospital components of the effect of mode of antibiotic administration.<sup>13,14</sup> The within-hospital effect measures the association of early transition to oral therapy and outcome once a child has selected a hospital and been admitted. The among-hospital effect measures the impact on outcome of transferring a given child from a hospital with lower-to-higher oral therapy use.<sup>15</sup> All analyses were conducted with SAS 9.1 (SAS Institute, Inc, Cary, NC) and Stata 8.0 statistical software (Stata Corp, College Station, TX).

### Human Subjects Oversight

The conduct of this study was approved by the CHCA and the Children's Hospital of Philadelphia Committee for the Protection of Human Subjects.

## RESULTS

### Subject Characteristics

A total of 6348 children had a diagnosis code of acute osteomyelitis or osteomyelitis unspecified during the study period (Fig 1). Children were excluded for significant problems with data completeness or quality as identified by PHIS (1056), insufficient follow-up time (1136), presence of comorbid conditions (1848), and length of stay  $\geq 10$  days.<sup>339</sup> This left 1969 children in the study cohort, of which 1021 had a central venous catheter placed for prolonged intravenous therapy and 948 did not and were assigned to the oral antimicrobial therapy group. The 2 study groups were virtually identical in terms of demographic characteristics, length of hospital stay, site of infection, infecting organism, surgical intervention, in-hospital antimicrobial therapy, and disease severity as measured by the case-mix index (Table 1). The proportion of children who had a central venous catheter placed for prolonged intravenous therapy varied significantly across hospitals from 10% to 95% ( $P < .001$ ; Fig 2).

### Treatment Failure

The overall treatment failure rate among the 1969 children was 4.7% (95% CI: 3.8%–5.7%; Table 2). The treatment failure rate varied across hospitals from as low as 1.8% to as high as 12.5% for hospitals with  $\geq 10$  children with acute osteomyelitis, but this variation was not statistically significant (likelihood ratio  $\chi^2 < 0.001$ ;  $P = .50$ ). The treatment failure rate was 5% (54 of 1021) in the prolonged intravenous therapy group and 4% (38 of 948) in the oral therapy group. There was no significant association between treatment failure and the

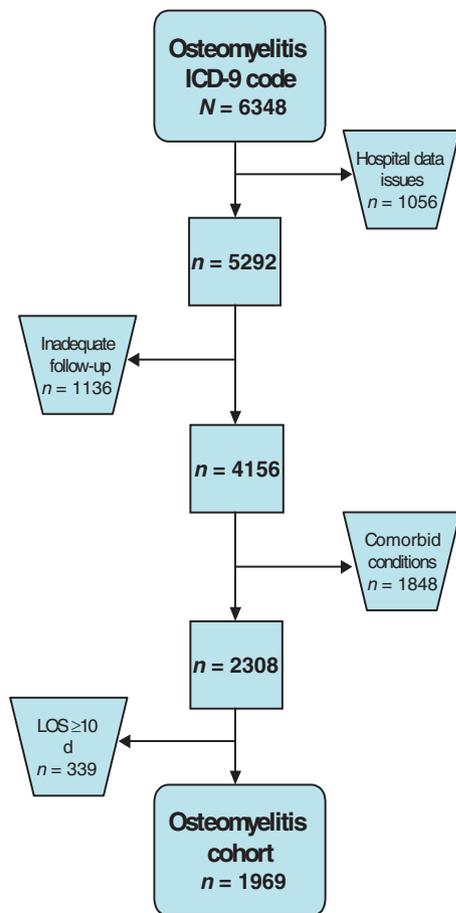


FIGURE 1  
Assembly of study cohort. LOS indicates length of stay.

mode of antimicrobial therapy adjusted for propensity score quintiles and clustering of observations within the 29 hospitals in the sample (odds ratio [OR]: 0.77 [95% CI: 0.49–1.22]; Table 2). The median time to treatment failure was similar in both groups, 16.5 days (interquartile range: 6.0–35.0 days) for the prolonged intravenous therapy group compared with 14.0 days (interquartile range: 3.0–45.0 days) for the oral therapy group ( $P = .65$ ). In addition, we did not detect any residual confounding after reinclusion of all of the covariates from the propensity score in the final multivariate analysis.

### Validation Study

Nineteen of the 29 hospitals agreed to participate in the validation study. Thirteen hospitals found no misclassification of the exposure, and 6 hospitals found that some children who were treated with prolonged intravenous therapy were misclassified and assigned to the oral therapy group. The rate of misclassification for these hospitals ranged from 11% to 50%. None of the hospitals reported misclassification of children assigned to the intravenous therapy group. Among the hospitals reporting no misclassification, the OR for treatment failure of oral therapy compared with intravenous therapy was 0.74 (95% CI: 0.27–2.02). Similar results were observed in the cohort of 16 hospitals that did not participate in the

TABLE 1 Demographic and Clinical Characteristics

Characteristics	Intravenous Therapy (N = 1021)	Oral Therapy (N = 948)
Age, n (%)		
0–1 y	86 (8)	77 (8)
1–5 y	343 (34)	322 (34)
>5 y	592 (58)	549 (58)
Length of hospital stay, median (interquartile range), d	5 (3–6)	4 (3–6)
Gender, n (%)		
Male	629 (62)	583 (62)
Race, n (%)		
White	725 (71)	676 (71)
Black	186 (18)	150 (16)
Other	66 (6)	80 (8)
Missing	44 (4)	42 (4)
Site, n (%)		
Shoulder	23 (2)	25 (3)
Upper arm	48 (5)	39 (4)
Forearm	31 (3)	34 (4)
Hand	38 (4)	38 (4)
Pelvic/thigh	315 (31)	287 (30)
Lower leg	247 (24)	245 (26)
Ankle/foot	182 (18)	178 (19)
Multiple sites	25 (2)	25 (3)
Unspecified	112 (11)	77 (8)
Organism, n (%) <sup>a</sup>		
Group A streptococcus	35 (3)	34 (4)
Streptococci, other	11 (1)	15 (2)
<i>S aureus</i>	351 (34)	291 (31)
Staphylococcus, other	51 (5)	33 (3)
Methicillin-resistant <i>S aureus</i>	83 (8)	62 (7)
<i>Escherichia coli</i>	2 (<1)	2 (<1)
Pneumococcus	12 (1)	9 (1)
Other Gram-negative organisms	9 (1)	5 (1)
>1 organism	89 (9)	73 (8)
Surgical procedure	377 (37)	314 (33)
Parental antibiotics received, n (%)		
Cefazolin	603 (59)	508 (54)
Oxacillin/naftillin	345 (34)	243 (26)
Vancomycin	188 (18)	83 (9)
Clindamycin	309 (30)	321 (34)
Trimethoprim-sulfamethoxazole	5 (<1)	6 (1)
Linezolid	2 (<1)	2 (<1)
Other <sup>b</sup>	355 (35)	216 (23)
Case mix index, median (interquartile range) <sup>c</sup>	1.67 (1.67–1.67)	1.67 (1.67–1.67)

<sup>a</sup> The listed organisms are not mutually exclusive. Children may have >1 organism recorded in their discharge record.

<sup>b</sup> Other antibiotics included the following: aminoglycosides, rifampin, extended-spectrum cephalosporins,  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations, quinolones, and doxycycline.

<sup>c</sup> All-Patient-Refined Diagnosis-Related Group classification included charge-based weight.

validation study or reported misclassification of the exposure (OR: 0.73 [95% CI: 0.47–1.13]).

### Within- and Among-Hospital Effects

The effect of mode of antimicrobial administration was deconstructed into within- and among-hospital effects. The within-hospital effect favoring oral therapy was 0.73 (95% CI: 0.39–1.35). There was also no among-hospital association of oral therapy and outcome (OR: 0.98 [95% CI: 0.93–1.04]).

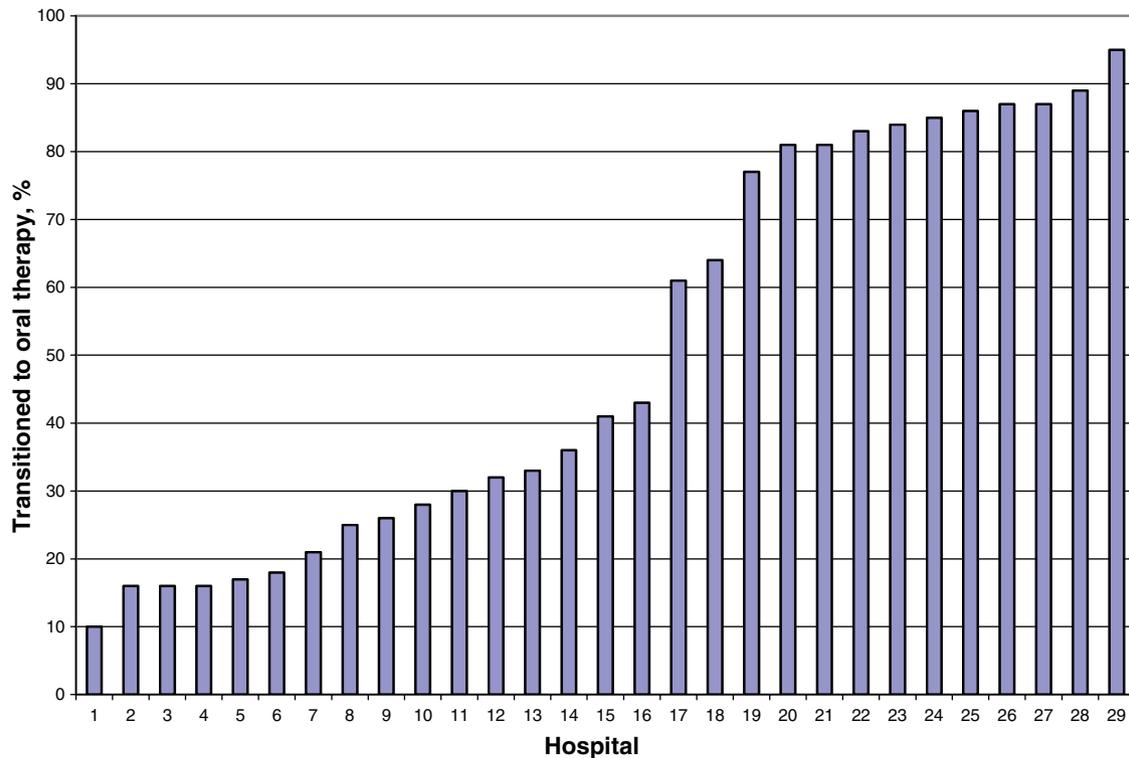


FIGURE 2  
Proportion of children in each hospital transitioned to oral therapy before discharge.

### Secondary Outcomes

Children treated with prolonged intravenous therapy were more likely to experience a treatment-related com-

**TABLE 2** Treatment Outcomes of Acute Osteomyelitis

Outcome	Intravenous Therapy (N = 1021), n (%)	Oral Therapy (N = 948), n (%)	Propensity Score-Adjusted OR (95% CI) for Those Children Treated With Early Transition to Oral Therapy
<b>Primary outcome</b>			
Treatment failure within 6 mo of diagnosis	54 (5)	38 (4)	0.77 (0.49–1.22)
Chronic osteomyelitis	13 (1.3)	8 (0.8)	0.84 (0.33–2.13)
Musculoskeletal surgery	18 (1.8)	15 (1.6)	0.80 (0.38–1.70)
Complication of osteomyelitis <sup>a</sup>	11 (1.1)	6 (0.6)	0.75 (0.27–2.07)
Acute osteomyelitis as sole readmission diagnosis	12 (1.2)	9 (0.9)	0.72 (0.25–2.08)
<b>Secondary outcomes</b>			
Any rehospitalization within 6 mo of diagnosis	102 (10)	56 (5.9)	0.6 (0.38–0.96)
Catheter-associated complication	35 (3)	0 (0)	—
Adverse effect of antimicrobial agents <sup>b</sup>	15 (1.5)	4 (0.4)	0.39 (0.14–1.1)

Analysis used the complete cohort. — indicates no data.

<sup>a</sup> Data include synovitis, pyogenic arthritis, sacroiliitis, disorders of bone and cartilage not otherwise specified, and disc disorder.

<sup>b</sup> Data include adverse drug reactions associated with antibiotics, *C difficile* infection, or agranulocytosis.

plication (Table 2). Thirty-five children (3%) in the prolonged intravenous treatment group were readmitted for a catheter complication. The rate of readmission for antimicrobial complications was significantly higher in the prolonged intravenous therapy group (1.6% vs 0.4%;  $P = .005$ ). The overall 6-month rehospitalization rate, which included hospitalizations for any reason (treatment failures, catheter complications, etc), was significantly higher in the prolonged intravenous therapy group compared with the oral therapy group (10.0% vs 6.0%;  $P = .017$ ).

### DISCUSSION

In this cohort of children with acute osteomyelitis, we found that use of prolonged intravenous therapy and early transition to oral therapy were equally effective. There was wide variation in the choice of treatment strategy across the 29 hospitals included in the cohort despite the fact that the children in the 2 treatment groups had identical clinical and demographic characteristics. The distribution of patients' age, gender, affected bone, and identified pathogen closely mirrors previous descriptions of the epidemiology of acute osteomyelitis in children.<sup>16–21</sup> The overall treatment failure rate of 4.2% in our study and in other reports<sup>6,7</sup> suggests that the study cohort is representative of children with acute, uncomplicated osteomyelitis and that our results, therefore, are likely generalizable to other cohorts of children with these clinical characteristics.

We anticipated that treatment selection decisions across hospitals may be influenced by observed severity

of illness or other patient characteristics, but this was not the case. The children in the 2 treatment groups were virtually identical in terms of their measured clinical and demographic characteristics. Thus, adjusted rates of treatment failure did not differ from crude rates. With identical patient characteristics and outcomes in the 2 treatment groups and such wide variability in treatment modality choice across hospitals, it seems that institutional culture and tradition, rather than patient characteristics, are driving therapeutic choices.

The lack of high-quality evidence supporting early transition to oral therapy has likely contributed significantly to the wide variability in its adoption. Several small observational studies have supported the use of short-course intravenous therapy with early transition to oral therapy as an adequate alternative to traditional management.<sup>3-8</sup> A systematic review that included 12 small studies (sample size ranging between 5 and 50 children), the majority of which were case series, demonstrated no statistically significant difference in clinical cure rate at 6 months between children receiving  $\geq 7$  days (98.8%) versus  $< 1$  week (95.2%) of intravenous antibiotics ( $P = .838$ ) before a transition to oral antimicrobial agents.<sup>7</sup> The treatment failure rates found in our large study were similar to those described in the systematic review.

We found a significant difference in the rate of rehospitalization for central venous catheter-associated complications in children treated with prolonged intravenous therapy after discharge. Approximately 4% of children treated with prolonged intravenous therapy experienced a catheter-associated complication requiring hospitalization. Previous studies that evaluated the complications of outpatient intravenous antimicrobial therapy showed high rates of central venous catheter-associated complications, ranging between 29% and 41%.<sup>8,22</sup> In this study, the rate of central venous catheter-associated complications is lower than these previous estimates but is likely an underestimate because it only captures children who required rehospitalization; emergency department visits were not captured.

A potential limitation of our study lies in misclassification in the administrative data, such as PHIS, because of miscoded or inaccurate information. For that reason, we validated the classification of exposure (intravenous or oral therapy) using chart review and showed that limiting the analysis to children from centers with no misclassification of the exposure variable did not change the relative risk of treatment failure. We recognize that misclassification of the outcome is also possible. Children could have been admitted to hospitals other than the PHIS hospitals for treatment failure or complication. However, we believe that most children who receive treatment for diseases such as osteomyelitis would likely return to the institution at which they received initial therapy. In addition, we cannot completely rule out a late occurrence of recurrent osteomyelitis or chronic osteomyelitis; however, we believe that the majority of complications should be captured in the 6-month follow-up period used in our study. Finally, some investigators have suggested that certain conditions must be

met for oral therapy to be considered for the treatment of acute osteomyelitis, including an identified organism, patient compliance, surgical debridement, and the ability to follow serum levels of the oral antibiotic.<sup>5,6,23,24</sup> We are unable to comment on patient compliance; however, we did not identify a difference between the 2 study groups in the number of patients with an identified organism or those who underwent surgery. In addition, serum levels of oral antibiotics are no longer routinely measured.

## CONCLUSIONS

We found that treatment of acute, uncomplicated osteomyelitis with early transition to oral therapy did not increase the risk of treatment failure. Our study may provide the best evidence to support wider use of this treatment strategy because, given the low treatment failure rates, a randomized, clinical trial might not be feasible. Clinical practice guidelines outlining parameters and a protocol for early transition to oral therapy need to be implemented across these hospitals to reduce variation and to determine whether good clinical outcomes are sustained.

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#### HEAD AND NECK INJURY RISKS IN HEAVY METAL: HEAD BANGERS STUCK BETWEEN ROCK AND A HARD BASS

**Objective:** To investigate the risks of mild traumatic brain injury and neck injury associated with head banging, a popular dance form accompanying heavy metal music.

**Design:** Observational studies, focus group, and biomechanical analysis.

**Participants;** Head bangers.

**Main outcome measures:** Head Injury Criterion and Neck Injury Criterion were derived for head banging styles and both popular heavy metal songs and easy listening music controls.

**Results:** An average head banging song has a tempo of about 146 beats per minute, which is predicted to cause mild head injury when the range of motion is greater than 75°. At higher tempos and greater ranges of motion there is a risk of neck injury.

**Conclusion:** To minimise the risk of head and neck injury, head bangers should decrease their range of head and neck motion, head bang to slower tempo songs by replacing heavy metal with adult oriented rock, only head bang to every second beat, or use personal protective equipment."

Patton D and McIntosh A. *BMJ* 2008;337:a2825. December 17, 2008

Noted by LRF, MD

## Prolonged Intravenous Therapy Versus Early Transition to Oral Antimicrobial Therapy for Acute Osteomyelitis in Children

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